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Impact of contralateral lymph nodal involvement and extranodal extension on survival of surgically managed HPV-positive oropharyngeal cancer staged with the AJCC eighth edition

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ABSTRACT

Objectives: Contralateral lymph node (LN) involvement is a prognostic factor in clinical staging of oropharyngeal squamous cell carcinoma (OPSCC), while pathologic nodal staging in the AJCC 8th edition for human papillomavirus-mediated OPSCC (HPV + OPSCC) focuses exclusively on the number of involved LNs (pLN+). This study assessed if the presence of contralateral pLN+ adds prognostic importance to the number of pLN+.

Materials and methods: The National Cancer Database was queried for pLN+ HPV + OPSCC treated with surgery with 10 or more LN dissected. Data were evaluated with Cox regression, propensity score matching (PSM), and Kaplan-Meier overall survival (OS) analysis.

Results: Of 3407 patients, 152 (4.5%) patients had contralateral pLN+. Subjects with contralateral pLN+ had higher pT/pN stage, more positive margins, extranodal extension (ENE), and lymphovascular invasion (LVI) (all $p < 0.05$). On univariate analysis, contralateral pLN+ trended toward worse OS (HR 1.58, 95% CI 0.98–2.55, $p = 0.061$). In the multivariable model (controlling for age, comorbidities, T-stage, N-stage, LN size, ENE, LVI, margin status and adjuvant therapy), LN laterality had no impact on OS (HR 0.87, 95% CI 0.52–1.45, $p = 0.520$). Further PSM analysis confirmed that contralateral pLN+ is not associated with OS in this population (HR 0.79, 95% CI 0.41–1.53, $p = 0.494$).

Conclusion: This study supports the AJCC 8th edition pathologic staging for HPV + OPSCC by observing that LN laterality is not associated with OS. ENE was associated with inferior OS and should be considered for future staging systems. Further study should be directed at the importance of nodal size in this population.

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is increasing in incidence, and now over 70% of cases diagnosed yearly in the United States are associated with Human papillomavirus (HPV) [1]. HPV associated OPSCC (HPV + OPSCC) represents a distinct disease compared to HPV-negative OPSCC. In general, HPV + OPSCC patients are younger, more likely to present with smaller tumors and advanced nodal disease, and have a more favorable prognosis compared to patients with HPV negative disease [2,3]. Because of these differences, a novel staging system has been dedicated specifically to HPV + OPSCC patients.

In a departure from their historical approach, for the 8th edition the American Joint Committee on Cancer (AJCC) created clinical and

Abbreviations: LN, lymph node; OPSCC, oropharyngeal squamous cell carcinoma; HPV, human papilloma virus; HPV + OPSCC, human papilloma virus mediated oropharyngeal squamous cell carcinoma; LVI, lymphovascular invasion; ENE, extranodal extension; OS, overall survival; HR, hazard ratio; CI, confidence interval; AJCC, American joint committee on cancer; RPA, Recursive Partitioning Analysis; NCDB, National Cancer Database

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pathologic staging systems for HPV + OPSCC that are based on substantially different criteria. The clinical N classification has been slightly modified, as a result of the ICON-S study, but is still fundamentally based on LN size and laterality [4]. However, in contrast to previous editions, the pathologic N classification for the AJCC 8th edition is not dependent on either of these factors (or others such as extranodal extension), and rather is solely dichotomized by the number of involved LNs (≤ 4 versus > 4), based primarily on a retrospectively assembled cohort from five cancer centers [5].

This divergence of the clinical and pathologic staging systems has raised concerns [6], and it is unclear whether contralateral nodal involvement adds to the prognostic information offered by AJCC 8th edition pathologic staging system, particularly since the presence of contralateral LNs is a strong predictor of distant failure and survival in the chemoradiation (CRT)-treated population [7]. To address this knowledge gap, we performed a propensity-matched analysis of a large, national database of surgically treated HPV + OPSCC patients.

Materials & methods

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding patient demographics, tumor characteristics, first-course treatment for the corresponding diagnosis, and survival for approximately 70% of the US population [8]. All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The data used in the study were derived from a de-identified NCDB file (2004–2015). As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were patients with newly diagnosed, pathologically proven pLN + HPV + OPSCC. The primary site codes used were C019 (base of tongue), C051 (soft palate), C052 (uvula), C090 (tonsillar fossa), C091 (tonsillar pillar), and C098 – C109 (tonsil NOS, vallecula, anterior epiglottis, lateral oropharyngeal wall, posterior oropharyngeal wall, branchial cleft, overlapping lesion of oropharynx, oropharynx NOS) and histology codes used were 8070 – 8079, 8052, 8083, 8084. HPV+ status was determined using CS_SITESPECIFIC_FACTOR_10 values of 020, 030, 040, 050, and 060. Of note, HPV positivity in the NCDB refers to high-risk type 16 or 18 by in situ hybridization, or positive immunohistochemical staining for p16 expression [9]. All patients were required to have been treated with curative-intent surgery (codes 20–90) with at least 10 dissected nodes. This threshold was chosen to select for patients undergoing dedicated neck dissection rather than excisional biopsy or limited nodal sampling, and it corresponds to the 10th percentile of total LN retrieved from patients enrolled on NRG Oncology RTOG trials 9501 and 0234 [10]. All patients included in the study were diagnosed in 2010–2015, and thus staged according to the AJCC 7th edition. Data from earlier years of diagnosis did not include HPV status, and thus was not included in this analysis. Patients with a pathologic nodal stage of N1, N2a, and N2b were included in the ipsilateral node cohort, and patients with a pathologic nodal stage of N2c in the contralateral LN cohort (of note, this includes patients with contralateral-only and bilateral nodal disease). AJCC 7th edition pN3 patients were excluded since LN laterality could not be determined. Other exclusion criteria were incomplete information on pathologic T and/or N classification (or in situ disease), patients without documented follow-up time, patients receiving non-standard adjuvant therapy (i.e. neoadjuvant therapy, adjuvant chemotherapy alone or adjuvant chemotherapy and radiation not given concurrently, (defined as a greater than 30 day interval in between the start dates of the respective treatments) and patients with a prior history of malignancy (Fig. 1).

In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data. The AJCC 8th edition pathologic N stage was determined based on the number of positive regional LN. Other variables included patient age, race, Charlson-Deyo comorbidity score (CDS), pathologic T stage, LN size, lymphovascular invasion (LVI), extranodal extension (ENE), surgical margin status, and adjuvant treatment. All statistical tests were two-sided, with a threshold of $p < 0.05$ for statistical significance, and were performed using STATA (version 13, College Station, TX). Univariate and multivariable Cox proportional hazards regression evaluated variables associated with overall survival (OS, defined from time of diagnosis to death, or censored at last contact). Covariates in the multivariable model were included if $p < 0.1$ on univariate analysis and added to the model in a forward stepwise fashion. After the cohort was divided based on contralateral LN disease (regardless of the presence of ipsilateral nodal involvement) versus lack thereof (e.g., ipsilateral LNs only), clinical characteristics were compared to evaluate differences between cohorts.

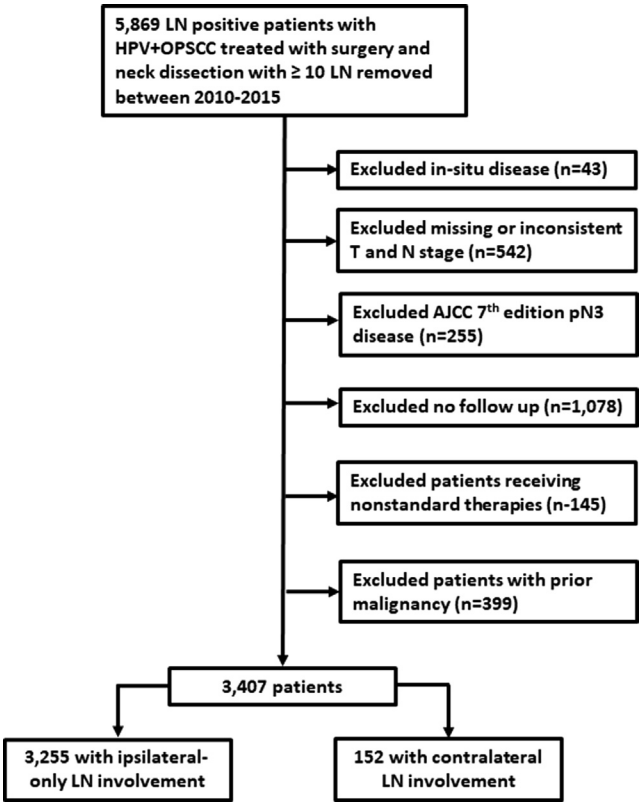

Fig. 1. CONSORT diagram delineating cohort selection.

Propensity score matching (PSM) was performed (using bootstrapping with 1-to-1 nearest-neighbor matching without replacement, caliper distance of 20% of the standard deviation of the pooled propensity scores) to identify matched cohorts representing patients with ipsilateral-only vs. contralateral lymph node involvement [11–13]. Matching was performed using variables associated with contralateral nodal disease on univariate logistic regression ($p < 0.1$). Covariate balance was evaluated using standardized differences of means. The survival analyses were repeated in the matched groups as described above for the unmatched cohort, adjusting for propensity quintile.

Results

A patient selection diagram is provided in Fig. 1. In total, 3407 patients with pathologically node-positive HPV + OPSCC were included (Table 1). Most patients were Caucasian (94.8%), male (86.6%), under the age of 65 (78.4%), and with T1-2 primaries (91.0%). Most patients were AJCC 8th edition pN1 (84.5%), with between 1 and 4 LN

Table 1
Cohort characteristics.

Variable	Total n = 3407	Ipsilateral Nodal Involvement n = 3255 (percentage)	Contralateral Nodal Involvement n = 152 (percentage)	χ^2 p-value
Age				0.873
< 65	2672 (78.4)	2552 (78.4)	120 (79.0)	
≥65	735 (21.6)	703 (21.6)	32 (21.1)	
Sex				0.404
Male	2949 (86.6)	2814 (86.5)	135 (88.8)	
Female	458 (13.4)	441 (13.6)	17 (11.2)	
Race				
White	3228 (94.8)	3080 (94.6)	148 (97.4)	0.387
Black	101 (3.0)	98 (3.1)	3 (2.0)	
Asian	28 (0.8)	27 (0.8)	1 (0.7)	
Other	50 (1.5)	50 (1.5)	0 (0)	
Comorbidities				
CDS 0	2785 (81.7)	2658 (81.7)	127 (83.6)	0.555
CDS > 0	622 (18.3)	597 (18.3)	25 (16.5)	
Tumor Subsite				< 0.001
Tonsil	2234 (65.6)	2171 (66.7)	63 (41.5)	
Base of tongue	1012 (29.7)	934 (28.7)	78 (51.3)	
Other	161 (4.7)	150 (4.6)	11 (7.2)	
Pathologic T stage				
T1	1692 (49.7)	1638 (50.3)	54 (35.5)	< 0.001
T2	1407 (41.3)	1349 (41.4)	58 (38.2)	
T3	224 (6.6)	198 (6.1)	26 (17.1)	
T4	84 (2.5)	70 (2.2)	14 (9.2)	
Pathologic N stage				< 0.001
N1	2879 (84.5)	2809 (86.3)	70 (46.1)	
N2	528 (15.5)	446 (13.7)	82 (54.0)	
LN Size				0.686
≤3 cm	2953 (86.7)	2823 (86.7)	130 (85.5)	
> 3 cm to ≤6 cm	173 (5.1)	163 (5.0)	10 (6.6)	
Unknown	281 (8.3)	269 (8.3)	12 (7.9)	
Grade				0.123
1	55 (1.6)	53 (1.6)	2 (1.3)	
2	1124 (33.0)	1082 (33.2)	42 (27.6)	
3	1799 (52.8)	1719 (52.8)	80 (52.6)	
Unknown	429 (12.6)	401 (12.3)	28 (18.4)	
Extranodal Extension				0.002
Absent	1961 (57.6)	1893 (58.2)	68 (44.7)	
Present	1268 (37.2)	1191 (36.6)	77 (50.7)	
Unknown	178 (5.2)	171 (5.3)	7 (4.6)	
Lymphovascular Invasion				0.001
Absent	2001 (58.7)	1931 (59.3)	70 (46.1)	
Present	885 (26.0)	826 (25.4)	59 (38.8)	
Unknown	521 (15.3)	498 (15.3)	23 (15.1)	
Margin Status				0.042
Negative	2676 (78.5)	2569 (78.9)	107 (70.4)	
Positive	643 (18.9)	603 (18.5)	40 (26.3)	
Unknown	88 (2.6)	83 (2.6)	5 (3.3)	
Adjuvant Treatment				< 0.001
None	566 (16.6)	551 (16.9)	15 (9.9)	
Radiotherapy	1262 (37.0)	1228 (37.7)	34 (22.4)	
Chemoradiotherapy	1501 (44.1)	1401 (43.0)	100 (65.8)	
Unknown	78 (2.3)	75 (2.3)	3 (2.0)	

involved. Of note, 152 (4.5%) patients had pathologic contralateral LN involvement. Of these 152 patients with pathologically positive contralateral LN, at least 86 (56.6%) had clinical evidence of contralateral nodal disease (AJCC 7th edition cN2c), 36 (23.7%) had AJCC 7th edition cN2b or lower disease, four (2.6%) had cN3 disease, and 26 (17.1%) did not have a complete clinical N stage recorded or were coded as unknown. Of the 117 total patients clinically staged as 7th edition N2c, 73.5% were also pathologically N2c. Compared to patients with pathologically positive ipsilateral nodal disease, a higher proportion of patients with contralateral pathologic LN involvement had pT3-4 disease (26.3% vs. 8.3%, $p < 0.001$) and AJCC 8th edition pN2 disease (54.0% vs. 13.7%, $p < 0.001$). In addition, patients with contralateral nodal disease were more likely to have base of tongue tumors (51.3% vs. 28.7%, $p < 0.001$), ENE (50.7% vs. 36.6%, $p = 0.002$) and LVI (38.8% vs. 25.4%, $p = 0.001$) compared to patients with ipsilateral-only LN involvement. Finally, 65.8% of patients with contralateral nodal disease received adjuvant CRT compared to 43.0% of patients with ipsilateral-only nodal disease ($p < 0.001$).

Table 2 shows the univariate and multivariable cox proportional hazards regression models. On univariable analysis, factors associated with worse OS were advanced age (per year HR 1.03, $p < 0.001$), greater comorbidities (CDS > 0 vs. CDS = 0 HR 2.08, $p < 0.001$), AJCC 8th edition pathologic N classification (pN2 vs. pN1 HR 2.59, $p < 0.001$), LN Size (> 3cm to ≤ 6 cm vs. ≤ 3 cm HR 1.85, $p = 0.005$)

Table 2
Univariate and multivariable cox proportional hazards regression models.

Variable	Univariate hazard ratio (95% CI)	P value	Multivariable hazard ratio (95% CI)	P value
Age (continuous)	1.03 (1.02–1.05)	< 0.001	1.02 (1.005–1.03)	0.009
Age			NA	
< 65	reference			
≥65	1.99 (1.54–2.57)	< 0.001		
Sex				
Male	reference		reference	
Female	0.66 (0.43–0.997)	0.048	0.76 (0.50–1.17)	0.212
Race			NA	
White	reference			
Black	1.26 (0.65–2.46)	0.491		
Asian	1.70 (0.63–4.55)	0.295		
Other	1.58 (0.65–3.83)	0.313		
Comorbidities				
CDS 0	reference		reference	
CDS > 0	2.08 (1.60–2.70)	< 0.001	1.74 (1.33–2.29)	< 0.001
Tumor Subsite				
Tonsil	reference		reference	
Base of tongue	1.19 (0.91–1.54)	0.206	1.20 (0.91–1.59)	0.195
Other	2.23 (1.38–3.59)	0.001	1.77 (1.08–2.92)	0.024
Pathologic T stage				
T1	reference		reference	
T2	1.88 (1.42–2.49)	< 0.001	1.74 (1.31–2.31)	< 0.001
T3	3.46 (2.35–5.09)	< 0.001	2.47 (1.66–3.70)	< 0.001
T4	4.30 (2.55–7.26)	< 0.001	3.05 (1.77–5.28)	< 0.001
AJCC 8th edition Pathologic N stage				
N1	reference		reference	
N2	2.59 (2.00–3.35)	< 0.001	1.97 (1.47–2.64)	< 0.001
LN Size				
≤3 cm	reference		reference	< 0.001
> 3 cm to ≤6 cm	1.85 (1.21–2.85)	0.005	2.02 (1.30–3.12)	0.002
Unknown	1.30 (0.87–1.94)	0.197	1.36 (0.90–2.04)	0.145
Grade				
1	reference		NA	
2	4.20 (0.58–30.17)	0.153		
3	4.14 (0.58–29.58)	0.157		
unknown	3.61 (0.49–26.55)	0.208		
Extranodal Extension				
Absent	reference		reference	
Present	2.04 (1.59–2.63)	< 0.001	1.66 (1.26–2.19)	< 0.001
Unknown	1.51 (0.88–2.59)	0.137	1.50 (0.87–2.61)	0.147
Lymphovascular Invasion				
Absent	reference		reference	
Present	1.83 (1.41–2.37)	< 0.001	1.28 (0.97–1.69)	0.076
Unknown	0.77 (0.51–1.15)	0.195	0.71 (0.47–1.06)	0.092
Margin Status				
Negative	reference		reference	
Positive	1.48 (1.12–1.96)	0.006	1.33 (0.997–1.78)	0.052
Unknown	1.49 (0.76–2.90)	0.245	1.38 (0.70–2.74)	0.357
Laterality				
Ipsilateral	reference		reference	
Contralateral	1.58 (0.98–2.55)	0.061	0.87 (0.52–1.45)	0.591
Adjuvant Treatment				
None	reference		reference	
Radiotherapy	0.53 (0.47–0.76)	0.001	0.58 (0.40–0.84)	0.004
Chemoradiotherapy	0.82 (0.60–1.13)	0.226	0.59 (0.42–0.83)	0.003
Unknown	1.65 (0.86–3.16)	0.130	1.52 (0.78–2.94)	0.217

pathologic T classification (pT2 vs. T1 HR 1.88, p < 0.001; pT3 vs. T1 HR 3.46, p < 0.001; pT4 vs. T1 HR 4.30, p < 0.001), tumor subsite (other vs. tonsil HR 2.23, p < 0.001), ENE (ENE + vs. ENE- HR 2.04, p < 0.001) LVI (LVI + vs. LVI- HR 1.83, p < 0.001), and margin status (positive margin vs. negative margin HR 1.48, p = 0.006). The presence of contralateral LNs had a trend towards worse survival on univariate analysis (Contralateral vs. ipsilateral only LN HR 1.58, 95% CI 0.98 – 2.55, p = 0.061).

Most variables significantly associated with worse survival on univariate analysis remained significant on multivariable analysis (Table 2). The correlation matrix of coefficients of the multivariable cox model showed that the variables in the model were not collinear (Supplemental Table 1). ENE remained strongly associated with worse survival (HR 1.66, 95% CI 1.26–2.19, p < 0.001) and LVI only trended to worse survival (LVI + vs. LVI- HR 1.28, p = 0.076). LN size > 3 cm also remained associated with worse survival (HR 2.02, 95% CI

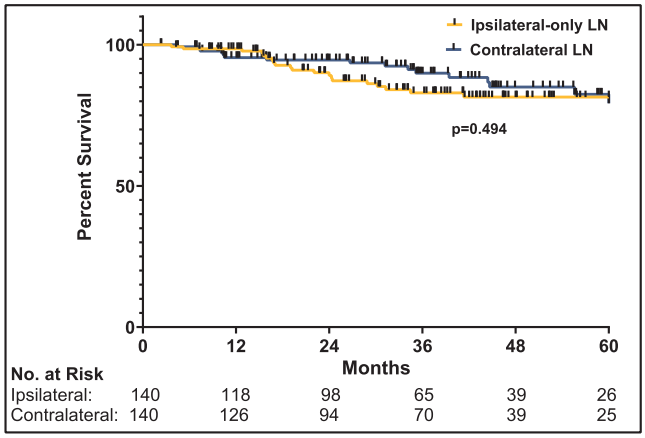

Fig. 2. Adjusted Kaplan Meier curve for overall survival of surgically managed HPV + OPSCC adjusted for propensity score matching on AJCC 8th edition T and N stage, tumor subsite, ENE, LVI, adjuvant treatment, and margin status.

1.30–3.12, p = 0.002). The presence of contralateral LN was not associated with survival on multivariable analysis (Contralateral vs. ipsilateral only LN HR 0.87, 95% CI 0.52–1.45, p = 0.591).

On univariate logistic regression, subjects with positive contralateral LNs were more likely to have higher AJCC 8th edition pathologic T and N classification, base of tongue subsite, positive margins, ENE, LVI, and to have received adjuvant CRT ($p < 0.05$ for all, Supplemental Table 2). The PSM generated a well-matched cohort of 280 patients, with 140 patients with contralateral nodal disease matched to 140 patients with ipsilateral-only nodal disease. The PSM showed a substantial reduction in the standardized percent bias across these covariates (Supplemental Fig. 1) indicating the propensity-matched groups were well balanced. On univariate Cox analysis after PSM, LN laterality still had no significant impact on survival OS (HR 0.79, 95% CI 0.41–1.53, p = 0.494). Fig. 2 shows the adjusted KM curve of ipsilateral vs. contralateral LN involvement after PSM.

Given that the proximity of the tumor towards midline has been felt to increase the risk of contralateral nodal involvement we evaluated tumors arising from lateralized structures (n = 2240 tonsil and lateral pharyngeal wall tumors) separately from tumors arising from midline structures (n = 1020 base of tongue, soft palate, uvula, anterior epiglottis, and posterior pharyngeal wall tumors). Primary sites of vallecula, branchial cleft, overlapping lesion of oropharynx or oropharynx not otherwise specified were not included in this portion of the analysis. Indeed, tumors arising from midline structures had a higher incidence of pathologic contralateral nodal disease compared to tumors arising from lateralized structures (7.8% vs. 2.8%, $p < 0.001$). When evaluating survival in the subset of patients with tumors arising from lateralized structures, lymph node laterality had no effect on survival on univariate analysis (contralateral vs. ipsilateral only LN HR 1.77, 95% CI 0.83–3.78, p = 0.139) or on multivariable analysis (contralateral vs. ipsilateral only LN HR 1.02, 95% CI 0.46–2.23, p = 0.966) after controlling for age, CDS, AJCC 8th edition pN and pT stage, LN size, ENE, LVI, margin status, and adjuvant therapy. When repeating this analysis in the subset of patients with tumors arising from midline structures, the same held true, and LN laterality was not associated with survival on univariate or multivariable analysis.

Discussion

This study utilizing a nationally representative database serves primarily to support the current AJCC 8th edition pathologic staging system for HPV+ oropharyngeal cancer by showing that lymph node laterality is not associated with survival in HPV + OPSCC patients managed with surgery. It also identifies other variables associated with poorer survival, namely ENE, that should be considered for incorporation into future staging systems.

The release of the 8th edition AJCC staging system was a long-awaited innovation for HPV+ oropharyngeal cancer. Previous studies had demonstrated that the 7th edition AJCC poorly discriminated prognosis for HPV+ patients [7,14] and that most patients were described as having stage IV disease despite high cure rates. The new staging system, which helped rectify these issues, was developed based upon the ICON-S study [4] (for clinical staging) and Haughey et al. [5] (for pathologic staging). Still however, the release of AJCC 8 was not without controversy. In a radical departure from previous editions in which pathologic staging represented a refinement of clinical staging, the 8th edition AJCC for pathologic staging is strikingly divergent from its clinical counterpart [6]. This is, at least in part, due to the independent analyses conducted for the clinical and pathologic staging systems.

The ICON-S study used a Recursive Partitioning Analysis (RPA) of 661 non-metastatic HPV + OPSCC patients to create the clinical staging framework, and then validated it with 1246 patients, most of whom (98%) were treated with definitive CRT [4]. The AJCC 8th edition clinical nodal staging system, developed from the ICON-S study, is simpler than the 7th edition, and has only three groups (cN1: ≥1 ipsilateral node ≤ 6 cm; cN2: contralateral or bilateral nodes ≤6 cm; cN3: any node > 6 cm). Although overall nodal stage in the 8th edition has less of an impact on overall stage group (ex. Patients with cN2 disease can still be designated stage II, whereas previously they were all stage IVA), the previous distinctions from the prior editions based upon the presence of contralateral adenopathy and size > 6 cm remained a fundamental part of the system. In contrast, in the pathological system node size and laterality are ignored while node number is the critical differentiator (pN1: 1–4 nodes; pN2: > 4 nodes). There is no pN3 stage, and stage is also unaffected by node location in relation to the primary tumor. This pathologic staging system based was based on a subgroup of 292 patients with ≥5 years of follow up that were treated with transoral surgery at select high volume surgical centers [5]. Notably, the authors did test the ICON-S system to their surgically managed patients but found overlap with the 95% CI of overall survival between different stage groups and that the c-index of ICON-S was lower than their proposed node-number-based staging paradigm.

Still, there were concerns about the robustness of the new system. For example, Haughey et al. reported that AJCC 7th edition pN2c (contralateral node involvement) patients had worse survival than pN1 and pN3 patients, though this was reportedly not statistically significant. However, when using N0 patients as a reference, only AJCC 7th edition N2c patients had worse survival on univariate analysis (HR 3.56, p = 0.049) whereas N1 (HR 0.89, p = 0.870), N2a (HR 1.24, p = 0.737), N2b (HR 1.89, p = 0.285), and N3 patients (HR 2.7, p = 0.174) had similar survival to N0 patients. Additionally, the number of patients with AJCC 7th edition pN2c disease was extremely small (n = 52), and pN2c patients were more likely to have pT3-T4 disease and > 4 lymph nodes involved, which may have been the true drivers of survival, though node laterality was ultimately not accounted for in a multivariable model. Finally, this study showed that on univariate analysis LVI (HR 1.92, p = 0.014) and PNI (HR 3.33, $p < 0.001$) were associated with worse overall survival, with a trend for worse survival in patients with ENE (HR 1.61, p = 0.060), but these variables were also not included in a multivariable model.

It is within the context of these controversies that the current study was undertaken. We sought to assess the importance of laterality in the context of pathologic node number in a larger nationally representative sample of patients, not be limited by surgical technique or confined to selected high-volume centers. The current study assesses the importance of both laterality and node number in a multivariable model. It demonstrates that on initial univariate analysis, the presence of pathologically positive contralateral lymph nodes trends to worse overall survival in HPV + OPSCC. However, after controlling for other

variables associated with survival in a multivariable Cox proportional hazards model (namely age, CDS, AJCC 8th edition pathologic T and N-stage, tumor subsite, LN size, LVI, ENE, margin status, and adjuvant therapy), the presence of pathologically positive contralateral lymph nodes is not associated with worse overall survival. The same effect holds true after propensity score matching, and thus these findings support the 8th edition AJCC staging system for HPV-mediated OPSCC.

Our results raise of the question of why laterality of involved nodes impacts survival and involved node number does not in patients treated with primary radiation-based treatment, while in surgically treated patients it is the opposite. While the NCDB data do not permit us to definitively ascertain the explanations for this difference, it may be that counting the number of involved nodes in clinically staged patients is fundamentally inaccurate, as it is known that many patients have additional lymph nodes involved pathologically that were not identified on preoperative imaging and exam findings [15]. In fact, in our study, 23.7% of patients with pathologically confirmed contralateral nodal disease were clinically staged as cN0, cN1, cN2a, or cN2b. Moreover, due to selection bias, patients undergoing surgery have on average smaller primary tumors, and a lower risk of locoregional failure than series including patients with T3 or T4 cancers referred for definitive radiation. Given that high node-number patients fail predominately distantly [16], node number may disproportionately drive the hazard risk for death when risk of locoregional failure is low.

Another important finding from this investigation is that ENE was independently associated with a poorer prognosis. ENE is not included in the AJCC 8th edition for pathologic nodal staging for HPV + OPSCC, although it has now been incorporated as part of HPV-negative OPSCC. This finding is supported by prior retrospective analyses which showed ENE to be predictive of poorer prognosis in HPV + OPSCC [17–19] and by a prospective study of HPV + OPSCC demonstrated that ENE patients had worse prognosis [20]. The ECOG 3311 and PATHOS trials will help further our understanding of the impact of ENE in a prospective fashion and with more granularity regarding the extent of ENE [21,22].

We also found that lymph node size of ≥ 3 cm is independently associated with worse prognosis. The present analysis of lymph node size, however, is limited, since our study was designed primarily to address the prognostic importance of LN laterality after controlling for LN number. Since patients with N3 disease (LN $>$ 6 cm) were excluded and the cutoff of 3 cm was chosen relatively arbitrarily based on the distinction between pN1 and pN2a in the AJCC 7th edition staging system, further study is needed to assess the importance of LN size on prognosis in this patient population.

Although the NCDB provides a unique platform with which to study this important clinical question, this investigation is not without limitations. The primary limitation is the small number of patients in this study (4.5%) that had contralateral nodal disease. This may be reflective of the clinical reality, as many patients with locoregionally advanced disease may be receiving primary CRT. Thus, it is important to note that these results may not be generalizable to patients who were otherwise selected for primary CRT. The intent of this study was not to support one treatment approach over another for patients with oropharyngeal cancer and bilateral or contralateral nodes, but rather to rigorously assess the new staging system. Second, a major limitation is the lack of information regarding laterality and type/technique of neck dissections, i.e. the NCDB does not code differently for bilateral or unilateral neck dissections. Furthermore, patients with pN3 disease were excluded due to the inability of determining LN laterality, so it is unknown if the presence of involved contralateral nodes in patients with N3 disease portends a worse prognosis. In addition, the specific chemotherapy regimens and the exact RT target (i.e. tumor bed alone vs. ipsilateral neck vs. bilateral neck) are not coded in the database. Finally, the extent of ENE is not reported in the NCDB, and it is possible that only ENE beyond a certain threshold may impact survival.

Conclusions

This novel study of a large, contemporary national database serves to validate the work that formed the basis for the new AJCC 8th edition staging system and supports its assertion that LN laterality does not appear to be independently associated with survival in this population. The presence of ENE was independently associated with inferior survival and should be considered in future pathologic nodal staging systems for HPV + OPSCC.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.104447.

References

[1] Mehanna H, Beech T, Nicholson T, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer–systematic review and meta-analysis of trends by time and region. Head Neck 2013;35(5):747–55.
[2] Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29(32):4294–301.
[3] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363(1):24–35.
[4] O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol 2016;17(4):440–51.
[5] Haughey BH, Sinha P, Kallogjeri D, et al. Pathology-based staging for HPV-positive squamous carcinoma of the oropharynx. Oral Oncol 2016;62:11–9.
[6] Fakhry C, Zevallos JP, Eisele DW. Imbalance between clinical and pathologic staging in the updated American Joint Commission on cancer staging system for human papillomavirus-positive oropharyngeal cancer. J Clin Oncol 2018;36(3):217–9.
[7] O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol 2013;31(5):543–50.
[8] Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15(3):683–90.
[9] Verma V, Simone 2nd CB, Lin C. Human papillomavirus and nasopharyngeal cancer. Head Neck 2018;40(4):696–706.
[10] Divi V, Harris J, Harari PM, et al. Establishing quality indicators for neck dissection: Correlating the number of lymph nodes with oncologic outcomes (NRG Oncology RTOG 9501 and RTOG 0234). Cancer 2016;122(22):3464–71.
[11] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 2011;46(3):399–424.
[12] Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Statistician 1985;39(1):33–8.
[13] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28(25):3083–107.
[14] Husain ZA, Chen T, Corso CD, et al. A comparison of prognostic ability of staging systems for human papillomavirus-related oropharyngeal squamous cell carcinoma prognostic ability of staging systems for HPV-related carcinomaprognostic ability of staging systems for HPV-related carcinoma. JAMA Oncol 2017;3(3):358–65.
[15] Koch WM, Ridge JA, Forastiere A, Manola J. Comparison of clinical and pathological staging in head and neck squamous cell carcinoma: results from Intergroup Study ECOG 4393/RTOG 9614. Arch Otolaryngol–Head Neck Surgery

2009;135(9):851–8.
[16] Lee NCJ, Kelly JR, Park HS, et al. Patterns of failure in high-metastatic node number human papillomavirus-positive oropharyngeal carcinoma. Oral Oncol 2018;85:35–9.
[17] An Y, Park HS, Kelly JR, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2017;123(14):2762–72.
[18] Kompelli AR, Morgan P, Li H, et al. Prognostic impact of high-risk pathologic features in HPV-related oropharyngeal squamous cell carcinoma and tobacco use. Otolaryngol Head Neck Surg 2018. 194599818818446.
[19] Zhan KY, Eskander A, Kang SY, et al. Appraisal of the AJCC 8th edition pathologic staging modifications for HPV-positive oropharyngeal cancer, a study of the National Cancer Data Base. Oral Oncol 2017;73:152–9.
[20] Ma DJ, Price K, Moore EJ, et al. Two-year results for MC1273, a phase 2 evaluation of aggressive dose de- escalation for adjuvant chemoradiation in HPV + oropharynx squamous cell carcinoma (OPSCC). Int J Radiation Oncol • Biol • Phys 2017;99(5):1320.
[21] Eastern Cooperative Oncology G, I. National Cancer. Transoral Surgery Followed By Low-Dose or Standard-Dose Radiation Therapy With or Without Chemotherapy in Treating Patients With HPV Positive Stage III-IVA Oropharyngeal Cancer. 2020 February; Available from: https://ClinicalTrials.gov/show/NCT01898494.
[22] Evans M, Knott S, Hurt C, et al. PATHOS: A phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for human papillomavirus (HPV)-positive oropharyngeal cancer. J Clin Oncol 2018;36(15_suppl). p. TPS6097-TPS6097.